PATENT COOPERATION TREATY

PCT

2 JAN2005

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
26213		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 03/00634	31/07/2003	01/08/2002
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 08 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[illegible]03/00634

A. CLASSIFICATION OF SUBJECT MAT
IPC 7 A61K38/43 A61K38/44 A61K38/45 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATTHEWS CHRISTOPHER C ET AL: "Enzymatic degradation protects neurons from glutamate excitotoxicity" JOURNAL OF NEUROCHEMISTRY, vol. 75, no. 3, September 2000 (2000-09), pages 1045-1052, XP001153216 ISSN: 0022-3042 the whole document --- -/--	1-4,26, 29-32, 54, 60-65, 87, 90-93, 115,116

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2004	10. 05. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thalmair, M

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSI[illegible]D TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIANG Z ET AL: "Glutamate is a principal mediator of HIV-1-infected immune competent human macrophage neurotoxicity" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-136.17, XP001156126 30th Annual Meeting of the Society of Neuroscience;New Orleans, LA, USA; November 04-09, 2000 ISSN: 0190-5295 the whole document	1-4,26, 29-32, 54, 60-65, 87, 90-93, 115,116
Y	DI GIORGIO, R.M. ET AL.: "Gabaergic systems in brain regions of glutamate-lesioned rats" ITALIEN JOURNAL OF BIOCHEMISTRY, vol. 34, no. 1, 1985, pages 19-28, XP009020661 page 19, line 15	1-4,26, 29-32, 54, 60-65, 87, 90-93, 115,116
Y	ENGELHARDT, P., AVENARIUS, H.J.: "The diagnostic value of enzyme determination in cerebrospinal fluid." MEDIZINISCHE KLINIK, MÜNCHEN, GERMANY, vol. 71, no. 17, 1976, pages 699-702, XP009020663 page 701	1-4,26, 29-32, 54, 60-65, 87, 90-93, 115,116
X	WO 99/21565 A (BLASS JOHN P ;CORNELL RES FOUNDATION INC (US)) 6 May 1999 (1999-05-06) claims 1,5,37,41 page 3, last paragraph -page 4, paragraph 1	1,29,60, 62,90, 119

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 03/00634

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-4 (part), 26 (part), 29 (part), 54 (part), 60-65(part), 87 (part), 90-93 (part), 115-116 (part), 119 (whole)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4 (part), 26 (part), 29-32 (part), 54 (part), 60-65 (part), 87 (part), 90-93 (part), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying transaminase (GPT).

2. Claims: 1-3 (part), 5 (whole), 26 (part), 29-31 (part), 33 (whole), 54 (part), 60-64 (part), 66 (whole), 87 (part), 90-92 (part), 94 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying dehydrogenase.

3. Claims: 1-3 (part), 6 (whole), 26 (part), 29-31 (part), 34 (whole), 54 (part), 60-64 (part), 67 (whole), 87 (part), 90-92 (part), 95 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying decarboxylase.

4. Claims: 1-3 (part), 7 (whole), 26 (part), 29-31 (part), 35 (whole), 54 (part), 60-64 (part), 68 (whole), 87 (part), 90-92 (part), 96 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying ligase.

5. Claims: 1-3 (part), 9 (whole), 26 (part), 29-31 (part),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

37 (whole), 54 (part), 60-64 (part), 70 (whole), 87 (part), 90-92 (part), 98 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying aminomutase.

6. Claims: 1-3 (part), 26 (part), 29-31 (part), 54 (part), 60-64 (part), 87 (part), 90-92 (part), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying racemase.

7. Claims: 1-3 (part), 8 (whole), 26 (part), 29-31 (part), 35 (whole), 54 (part), 60-64 (part), 69 (whole), 87 (part), 90-92 (part), 97 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one glutamate modifying transferase.

8. Claims: 1 (part), 10-11 (whole), 16 (whole), 26 (part), 29 (part), 38-39 (whole), 44 (whole), 54 (part), 60-62 (part), 71-72 (whole), 77 (whole), 87 (part), 90 (part), 99-100 (whole), 105 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one co-factor of a glutamate modifying enzyme alone or in combination with a glutamate modifying enzyme.

9. Claims: 1 (part), 12-15 (whole), 17-25 (whole), 26 (part), 29 (part), 40-43 (whole), 45-53 (whole),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

60-62 (part), 73-76 (part), 78-86 (whole), 87 (part), 90 (part), 101-104 (whole), 106-114 (whole), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and/or a cofactor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate optionally including further a glutamate modifying enzyme.

10. Claims: 1 (part), 26 (part), 27-28 (whole), 29 (part), 54 (part), 55-56 (whole), 60-61 (part), 62 (part), 87 (part), 88-89 (whole), 90 (part), 115-116 (part), 117-118 (whole)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels, wherein said agent is at least one inhibitor of a glutamate synthesizing enzyme.

11. Claims: 1 (part), 26 (part), 54 (part), 57-59 (whole), 60-62 (part), 87 (part), 90 (part), 115-116 (part)

a method of reducing extracellular brain glutamate levels, and the corresponding pharmaceutical compositions comprising as an active ingredient, pyruvate and oxaloacetate in a concentration suitable for reducing blood glutamate levels and a pharmaceutically acceptable carrier.

12. Claims: 1(part), 29 (part), 60 (part), 62 (part), 90 (part), 119 (whole)

Pharmaceutical composition for reducing extracellular brain glutamate levels, comprising, as an active ingredient, oxaloacetate diethylester capable of reducing blood glutamate levels and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 03/00634

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921565 A	06-05-1999	AU 760140 B2	08-05-2003
		AU 9213998 A	17-05-1999
		CA 2306875 A1	06-05-1999
		EP 1032403 A1	06-09-2000
		JP 2001521002 T	06-11-2001
		WO 9921565 A1	06-05-1999
		US 2003176365 A1	18-09-2003
		US 6537969 B1	25-03-2003